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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/667,570	09/22/2003	Garth Boehm		1970

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PATRICK J. HALLORAN, PH.D., J.D
3141 MUIRFIELD ROAD
CENTER VALLEY, PA 18034

EXAMINER	
SHEIKH, HUMERA N	

ART UNIT	PAPER NUMBER
1615	

MAIL DATE	DELIVERY MODE
07/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/667,570	BOEHM ET AL.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,15-24,37-39,45 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,15-24,37-39,45 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt of the Request for Continued Examination (RCE) under 37 C.F.R. 1.114 filed 11/18/08 and the Amendment and Applicant's Arguments/Remarks, both filed 04/06/09 is acknowledged.

Claims 1-10, 15-24, 37-39, 45 and 46 are pending in this action. Claim 1 has been amended herein. Claims 47-48 have been cancelled herein. Claims 11-14, 25-36 and 40-44 were previously cancelled. Claims 1-10, 15-24, 37-39, 45 and 46 are rejected.

* * * * *

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06 April 2009 has been entered.

* * * * *

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-10, 15-24, 37-39, 45 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Palermo (WO 99/32120).

Palermo (WO '120) teaches an oral dosage form of an opioid analgesic, comprising an analgesically effective amount of an opioid agonist together with an opioid antagonist, the amount of opioid antagonist including being sufficient to counteract opioid effects if extracted together with the opioid agonist (see p. 6, lines 1-18). The oral dosage forms of the invention are sustained release formulations (p. 8, lines 1-9).

In preferred embodiments, the opioid agonist is hydrocodone, hydromorphone, oxycodone, morphine or pharmaceutically acceptable salts thereof (p. 7, lines 5-6); (p. 13, lines 14-27). Palermo teaches that the dosage forms of the invention may be liquids, tablets, multiparticulates, dispersible powders or granules, hard or soft capsules, lozenges, aqueous or oily suspensions, emulsions, syrups, elixirs, microparticles, buccal tablets, etc. (p. 7, lines 27-31); (p. 8, line 29 – p. 9, line 1). In certain preferred embodiments, the oral dosage forms are sustained release formulations. This may be accomplished via the incorporation of a sustained release carrier into a matrix containing the opioid agonist and opioid antagonist; or via a sustained release coating of a matrix containing the opioid agonist and opioid antagonist, where

the sustained release coating contains at least a portion of the sustained release carrier included in the dosage form (p. 8, lines 1-9); (p. 20, lines 16-21).

Palermo teaches that the dosage forms may be coated with one or more materials suitable for the regulation of release or the protection of the formulation. The coatings are provided to permit either pH-dependent or pH-independent release. A pH-dependent coating serves to release the opioid in desired areas of the gastrointestinal tract, such that an absorption profile is provided which is capable of providing at least about eight hours and preferably about twelve hours to up to about twenty-four hours of analgesia to a patient (p.21, lines 18-29).

Suitable pH-dependent coatings taught include shellac, methacrylic acid ester copolymers, zein and the like (p.22, lines 2-5).

In preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) containing the opioid analgesic is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer or (iii) mixtures thereof (p. 22, lines 6-14).

Suitable and preferred alkylcellulose polymers taught include ethylcellulose (p. 22, lines 19-25). Acrylic polymers are also disclosed and include acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid) and the like. In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties (p. 23, line 10 – p. 24, line 22); (p. 29, lines 7-18).

Plasticizers are also included in the composition. Suitable plasticizers taught include triethyl citrate, tributyl citrate, dibutyl phthalate, polyethylene glycols, propylene glycol, diethyl phthalate, castor oil and triacetin (p. 24, line 24 – p. 25, line 20).

A process for preparing coated beads is disclosed at p. 25, line 21 – p. 28, line 8, wherein it is stated that the controlled release profile of the formulations can be altered, for example, by varying the amount of overcoating with the hydrophobic material, altering the manner in which the plasticizer is added to the hydrophobic material, by varying the amount of plasticizer relative to the hydrophobic material, etc. The dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating (p. 26, lines 2-4). Matrix bead formulations are disclosed at page 28. Hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials and any pharmaceutically acceptable hydrophobic material or hydrophilic material, which is capable of imparting, controlled release of the active agent and which melts (or softens to the extent necessary to be extruded) may be used in this invention (p. 28, lines 19-30).

Hydrophobic materials disclosed include alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, shellac, zein, hydrogenated castor oil, hydrogenated vegetable oil or mixtures thereof (p. 29, lines 7-9). The hydrophobic material can also be selected from materials such as hydroxyalkylcelluloses, such as hydroxypropylmethyl cellulose (p. 29, lines 9-18). In one embodiment, the ratio of the at least one hydroxyalkylcellulose or acrylic resin to the at least one aliphatic alcohol/polyalkylene glycol determines to a considerable extent, the release rate of the opioid from the formulation (p. 29, line30 – p. 30, line 3).

It is noted that Palermo does not explicitly teach the instant dissolution profiles as claimed by Applicant. However, it is the position of the Examiner that suitable release rates or dissolution profiles can be determined by one of ordinary skill in the art through routine or manipulative experimentation to obtain optimal results as these are variable parameters attainable within the art. No unexpected or superior results have been demonstrated, which accrue from the instant dissolution profiles. The Palermo reference explicitly recognizes and teaches oral dosage forms comprising opioid analgesics whereby the dosage forms are effective for the substantial reduction of pain for a twenty-four hour duration period.

Regarding new claims 45 & 46, Palermo teaches that suitable coating materials taught include, for example, hydroxypropylcellulose as well as combinations of hydrophobic materials (page 30, lines 8-17). The reference additionally teaches excipients, such as wetting agents and emulsifiers (p. 7, lines 16-26) and thus would include sodium lauryl sulphate.

Thus, given the teachings of Palermo discussed above, the instant invention, when taken as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

* * * * *

Claims 1, 4-10, 15-24, 37-39, 45 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller *et al.* (U.S. Pat. No. 6,326,027).

Miller *et al.* ('027) teach a controlled release preparation for oral administration that contains the opioid analgesic – tramadol, or a pharmaceutically acceptable salt thereof, as active ingredient (see Abstract); (col. 1, lines 1-22). The oral controlled release tramadol preparation is suitable for at least twelve-hourly (e.g., up to twenty-four hourly) administration for the treatment of pain (col. 1, lines 23-25); (col. 7, lines 54-67).

To allow for controlled release tramadol over at least a twelve hour period following oral administration, the in vitro release rate corresponds to the percent rate of tramadol release, as shown, for instance, in Table 1 (col. 1, lines 40-55). Table 1 demonstrates the following release:

Time (H)	% Released
1	0-50
2	0-75
4	3-95
8	10-100
12	20-100
16	30-100
24	50-100
36	>80

Other preferred tramadol preparations demonstrating in vitro release rates are exemplified in Tables 2-4, shown on columns 1-2.

The controlled release preparation may be presented in the form of granules, spheroids, pellets, multiparticulates, capsules, tablets, sachets, controlled release suspensions and the like (col. 3, lines 32-37).

The active ingredient may be suitably incorporated in a matrix, preferably a controlled release matrix (col. 3, lines 38-46).

Suitable materials for inclusion in a controlled release matrix include hydrophilic or hydrophobic polymers, such as gums, cellulose ethers, acrylic resins and protein derived materials. Of these polymers, the cellulose ethers, especially alkylcelluloses are preferred (col. 3, line 47 – col. 4, line 13). Additional hydrophobic materials taught include hydrogenated vegetable oil, hydrogenated castor oil and waxes (col. 5, lines 49-58). Release modifying agents taught include polyethylene glycol (col. 5, lines 59-62).

Other pharmaceutically acceptable ingredients taught that may contribute to controlled release properties include hydroxyalkylcelluloses such as hydroxypropylmethyl cellulose or water insoluble polymers, such as acrylic polymers or copolymers, for example, ethylcellulose (col. 4, lines 36-44); (col. 7, lines 33-37). Water-soluble polymers such as polyvinylpyrrolidone are also disclosed (col. 4, lines 45-55).

The controlled release matrix can also contain surfactants, glidants, e.g., dibutyl sebacate (plasticizer) (col. 4, lines 13-19).

The Examples at columns 8-13 demonstrate various tramadol tablets and preparations of the invention.

While Miller *et al.* do not explicitly teach the instant dissolution profiles as claimed by Applicant, it is the position of the Examiner that suitable release rates or dissolution profiles can

be determined by one of ordinary skill in the art through routine or manipulative experimentation to obtain optimal results as these are variable parameters attainable within the art. No unexpected or superior results have been demonstrated, which accrue from the instant dissolution profiles. The Miller *et al.* patent explicitly teaches controlled release dosage forms comprising an opioid analgesic, which provide analgesia effects for the treatment of pain for a twenty-four hour period or greater. The preparations taught by Miller *et al.* provide for very low release rates of active ingredient, e.g., corresponding to release over a period of greater than 24 hours, such as more than 36 hours.

Regarding new claims 45 & 46, Miller teaches the use of hydroxypropylcellulose as well as surfactants such as sodium lauryl sulfate. See column 4, lines 39-44 and col. 7, lines 39-43.

Thus, given the teachings of Miller *et al.* discussed above, the instant invention, when taken as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

* * * * *

Response to Arguments

Applicant's arguments filed 04/06/09 have been fully considered but were not found persuasive.

- **Rejection under 35 U.S.C. §103(a) over Palermo (WO 99/32120):**

Applicant argued, "While the Examiner did discuss the various sustained release components and formulations presented by Palermo, the thrust of the rejection is that because such components were known in the art, Applicants oral dosage form (exhibiting a previously unknown release profile) was also known. In addition, the Examiner has not shown that

one of skill in the art would have been motivated to produce the instantly claimed oral dosage forms. Applicants do not believe this rejection is proper."

Applicant's arguments have been considered, but were not found persuasive. While Palermo does not teach Applicant's claimed dissolution profile, the reference nonetheless recognizes and teaches that their dosage forms may be coated with one or more materials suitable for the regulation of release or for protecting the formulation. The coatings provided by Palermo permit either pH-dependent or pH-independent release. Palermo teaches that the dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating (p. 26, lines 2-4). Suitable coating materials disclosed include, for example, hydroxypropylcellulose as well as combinations of hydrophobic materials (page 30, lines 8-17). The reference additionally teaches excipients, such as wetting agents and emulsifiers (p. 7, lines 16-26). The reference further teaches that the formulation is capable of providing at least about eight hours and preferably about twelve hours to up to about twenty-four hours of analgesia to a patient (p.21, lines 18-29). Thus, while the reference does not teach the exact release rate claimed, the Palermo publication is clearly suggestive of attaining a therapeutic, analgesic effect for up to twenty-four hours and specifically teaches sustained release formulations. Hence, no superior results are seen in Applicant's claimed dissolution rate, as the art vividly teaches the same duration of therapeutic effect as that desired by Applicant and further teaches the use of sustained release coating materials for controlled delivery of active agent. The reference further suggests that the dissolution profile of the end product may be modified, such as by increasing or decreasing the thickness of the retardant coating. It is the position of the Examiner that it would be well within the purview of one of ordinary skill in the

art to determine suitable or effective rates of release or dissolution profiles via routine experimentation to obtain optimal results as these are variable parameters attainable within the art. The reference vividly recognizes formulations comprising the use of an opioid agonist provided in sustained release form for the substantial reduction of pain in order to achieve therapeutic activity for a twenty-four hour duration period.

- **Rejection under 35 U.S.C. §103(a) over Miller (USPN 6,326,027):**

Applicant argued, "While the Examiner did discuss the various sustained release components and formulations presented by Miller, the thrust of the rejection is that because such components were known in the art, Applicants oral dosage form (exhibiting a previously unknown release profile) was also known. In addition, the Examiner has not shown that one of skill in the art would have been motivated to produce the instantly claimed oral dosage forms. Applicants do not believe this rejection is proper".

Applicant's arguments have been considered, but were not found persuasive. The Miller patent explicitly teaches controlled release dosage forms comprising an opioid analgesic, which provide analgesia effects for the treatment of pain for a twenty-four hour period or greater, as is also desired by the instant invention. The preparations taught by Miller provide for very low release rates of active ingredient. Based on Table 1 disclosed by Miller, (reproduced below for Applicant's convenience), Miller would be fully capable of meeting the instant dissolution profile claimed by Applicant, which is "less than about 10% within about 6 hours and at least about 60% within about 24 hours..." (Instant Claim 1). As is seen from the Table, Miller teaches that at 8 hours about 10-100% is released. Thus, based on this table, it would be likely that less

than 10% would be released within a 6-hour time period. At 24 hours, Miller teaches that 50-100% is released, which would also meet and fall within Applicant's limitation of "at least about 60% release within about 24 hours...". Thus, while the art does not explicitly teach Applicant's exact claimed rates of release, the art clearly suggests release rates that fall within and/or overlap with the release ranges/rates claimed by Applicant and thus meets Applicant's instant rates of release. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). Absent a showing of evidence to the contrary, the formulations of Miller, which provide for use of the same ingredients with dissolution rates that overlap and/or fall within those claimed by Applicant, would achieve the same beneficial results as instantly sought by Applicant.

Table 1 of Miller:

Time (H)	% Released
1	0-50
2	0-75
4	3-95
8	10-100
12	20-100
16	30-100
24	50-100
36	>80

Conclusion

--No claims are allowed at this time.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday- Friday during regular business hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Humera N. Sheikh/

Primary Examiner, Art Unit 1615

hns

June 30, 2009